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SOME CONSIDERATIONS ON THE STRUCTURE OF THE QUADRUPED EXTREMITIES—*N. Rashevsky* - - - - - - - - - - - 83

TREE TRUNKS AND BRANCHES AS OPTIMUM MECHANICAL SUPPORTS OF THE CROWN: II. THE BRANCHES—*Martinus H. M. Esser* - - - - - - - - - - - - - - - - - - 95

THE PROBABILISTIC APPROACH TO THE EFFECTS OF RADIATIONS AND VARIABILITY OF SENSITIVITY—*I. Opatowski* - - - - - 101

ON THE RELATIONSHIP BETWEEN RESPONSE TIME AND DOSAGE OF A DRUG AS A FUNCTION OF ITS MODE OF ENTRY—*H. D. Landahl* - - - - - - - - - - - - - - - - - - - 121

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BULLETIN OF
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SOME CONSIDERATIONS ON THE STRUCTURE OF QUADRUPED EXTREMITIES

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An attempt is made to develop a general theory of the structure of an extremity of a quadruped or biped, based on its mechanical function. The problem is essentially one of dynamics of a chain of linked levers. The equations of motions of such systems are practically insoluble exactly at the present time. A very crude approximation method is therefore outlined. It is shown that, theoretically, the number of links in the chain forming the extremity may be determined by the optimum use of the total available force of the flexors and extensors. Discussion of the formula derived from this point of view shows, however, that actually this is not the determining factor. Other theoretical possibilities are discussed. While no application can be made at present, yet in principle it is shown how mechanical consideration can throw light on the anatomical structure of the extremity.

In a previous publication we derived a relation between the maximum speed of locomotion of an animal and the length of its extremities. We have found physical reasons for the necessity of the extremities to be "folding" and to consist of at least two parts. Actually the structure of the quadruped extremity is more complex, although in most cases it may be considered within a rough approximation to consist of three parts: the hip, the ankle and the foot. In man the last is much shorter than either of the first two parts, yet in running the foot is still used as a lever, and not merely as a supporting surface for giving better contact with the ground. In some animals, as the elephant, the size of the foot is also rather small, compared to the size of the hip and ankle. In most other animals, however, especially in such as the horse, the dog, and the camel, the foot is as long as or even longer than that of the hip. Thus in the most general case the extremity may be roughly considered as consisting of three linked levers. Inasmuch as a system of two linked levers is sufficient to provide for a "repelling" mechanism, one of the problems which we confront is to find a mechanical reason for the general existence of three lever chains.

Before we can hope to reach any conclusions that are applicable to reality, we must again make a purely theoretical study of different possible situations. This paper is the first step towards such a study.

A general dynamics of chains of levers was developed long ago by O. Fischer (1893) [cf. also Winkelmann and Grammel, 1927]. While the equations of motion of such a system are readily established, their integration even in simple cases presents almost insuperable difficulties, and recourse must be had to very drastic approximations.

In attempting a dynamical theory of the action of an extremity as a mechanism which acts to repel the body from the ground, we must remember that strictly speaking we cannot consider an extremity alone. We have to consider the whole organism as one system of linked levers. For such a system each equation of motion contains terms involving all other members of the system. Perhaps a possible simplification of the problem may be obtained by considering the oversimplified two-dimensional system represented on Figure 1. Here

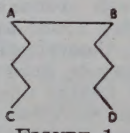

FIGURE 1

the member AB plays roughly the part of the trunk, while AC and BD represent correspondingly the rear and front extremity, each consisting in general of n levers. Some fundamental properties of the corresponding real three-dimensional systems may probably be approximately explained by such a schematized picture. Mathematically it has the great advantage of being a non-branching chain of levers, while actually any animal is a branching chain.

However, even an approximate treatment of such a two-dimensional system represents still rather great difficulties. Therefore, we shall make here a further simplification, suggesting subsequently a possible method for handling the system represented in Figure 1.

We shall schematize our picture further by considering only one extremity, consisting of n links, and by assuming that the mass M of the whole organism, minus that of the extremity, is concentrated near the upper end of the uppermost link. We shall number the links consecutively, beginning with the lowest, whose lowermost point is in contact with the ground (Figure 2). During the repelling action of the extremity this lowermost point P_1 remains fixed.

We shall denote the mass of the ith link by m_i, its length by l_i. The position of each link is given by the angle ϕ_i, as indicated in Figure 2.

We shall make further the following simplifications. We shall assume that each joint is actuated by muscles belonging to the nearest proximal link, that is, the ith joint is actuated by muscles belong-

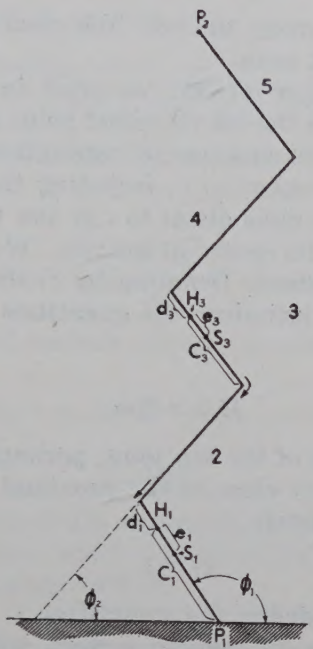

FIGURE 2

ing to the $(i+1)$st link (Figure 3). Actually the moment of the muscular force with respect to the axis of the joint varies with the angle which the two links make at the joint (O. Fischer, 1893). We shall, however, assume that this moment is independent of the angle and equal to the product of the constant muscular force $F_{i,i+1}$ of the ex-

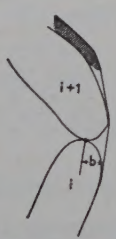

FIGURE 3

tensor muscle $i + 1$, by the constant shoulder b, which we assume the same for all joints. All the torques $b F_{i,i+1}$ act in such a way, that they tend to rotate the links with $\phi_i > \pi/2$ clockwise, those with $\phi_i < \pi/2$ counterclockwise. The latter direction of rotation will be considered as positive. Moreover we shall consider that at the point P_2 of the nth link, in which the mass M is concentrated, a torque Fb

is applied, tending to move the nth link clockwise if n is odd, and counterclockwise if n is even.

Following O. Fischer (1893) we shall introduce the following notations. We shall call the ith principal point H_i the center of gravity of a system, which is obtained by concentrating the masses of all links, proximal with respect to i, including the mass M, at the ith joint, the masses of all links distal to i at the $(i-1)$st joint, and the mass of the ith link at its center of gravity. We shall call such a system the ith reduced system. Denoting by S_i the center of gravity of the ith link, we shall introduce the quantities c_i and d_i, which are defined in Figure 2.

If, as we assume

$$M >> \sum m_i , \tag{1}$$

then with the exception of the nth joint, perhaps, the principal points of each link will lie very close to the proximal end of that link, and thus we have approximately

$$c_i = l_i . \tag{2}$$

Furthermore, we define the quantities λ_i as follows: λ_i is the radius of inertia of the ith reduced system, with respect to the axis passing through the ith joint. We also put

$$M + \sum m_i = M_0 . \tag{3}$$

Because of inequality (1), we have approximately

$$M = M_0 . \tag{4}$$

Let a_{ik} be an element in the ith row and kth column of the symmetric matrix

$$\begin{matrix} \lambda_1^2 & l_1c_2 & l_1c_3 & \cdots & l_1c_n \\ l_1c_2 & \lambda_2^2 & l_2c_3 & \cdots & l_2c_n \\ l_1c_3 & l_2c_3 & \lambda_3^2 & \cdots & l_3c_n \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ l_1c_n & l_2c_n & \cdots & & \lambda_n^2 , \end{matrix} \tag{5}$$

and let

$$B_i = -M_0 g c_i \cos \phi_i . \tag{6}$$

Consider a deformation of the system, in which the ith link is rotated by the angle $d\phi_i$, while all distal links remain stationary and all proximal are subject to a pure translation, so that none of the angles ϕ_k, $k \leq i$ is changed. Then $B_i d\phi_i$ represents the work done in such a displacement by the force of gravity. The work done by the torque $b F_{i-1,i}$ in such a displacement is

$$(-1)^{n+i+1}\, b\, F_{i-1,i}\, d\phi_i\,,$$

the work done by the torque $b\, F_{i,i+1}$ is

$$(-1)^{n+i+1}\, b\, F_{i,i+1}\, d\phi_i\,. \tag{7}$$

The work done in the displacement $d\phi_i$ by all other torques $b\, F_{kl}$ is zero.

Denote

$$A_i = M_0 \sum_{k=1}^{k=n} a_{ik}\left[\cos(\phi_i - \phi_k)\,\frac{d^2\phi_k}{dt^2} + \sin(\phi_i - \phi_k)\left(\frac{d\phi_k}{dt}\right)^2\right]. \tag{8}$$

Then the equations of motion of the system here considered are (Fischer, 1893):

$$A_i = -B_i + (-1)^{n+i+1}\,(b\, F_{i-1,i} + b\, F_{i,i+1})\,. \tag{9}$$

Let

$$l = \sum l_i\,, \tag{10}$$

then, by a similar approximate argument, as used before (Rashevsky, 1944), the time Δt during which the extremity exerts its repelling action is of the order of magnitude of

$$\Delta t \sim l/v, \tag{11}$$

where v is the velocity of locomotion.

Let, during Δt the angles ϕ_i vary on the average by the amounts $\bar{\phi}_i$. Then the average angular velocities are of the order of $\bar{\phi}_i/\Delta t = \bar{\phi}_i\, v/l$, and the average accelerations are of the order of $\bar{\phi}_i\, v^2/l^2$.

In the final extended state of the extremity the values $\phi_i - \phi_k$ all become zero; hence, the cosine terms become equal to one, and the sine terms vanish. If we consider the case, when initially the values of $\phi_i - \phi_k$ were not too large, we may very roughly consider during the process of extension all $\cos(\phi_i - \phi_k)$ terms as well as all $\sin(\phi_i - \phi_k)$ terms as constant, with values between zero and one. We may do the same thing for $\cos\phi_i$ in the expression for B_i.

Putting

$$\cos(\phi_i - \phi_k) = \alpha_{ik}; \quad \sin(\phi_i - \phi_k) = \beta_{ik}; \quad \cos\phi_i = \gamma_i; \tag{12}$$

and averaging the equation (9) by substituting

$$\dot{\phi}_i = \bar{\phi}_i\, v/l; \quad \ddot{\phi}_i = \bar{\phi}_i\, v^2/l^2, \tag{13}$$

we obtain the following system

$$\frac{M_0\, v^2}{l^2}\sum_k a_{ik}(\alpha_{ik}\,\bar{\phi}_i + \beta_{ik}\,\bar{\phi}^2{}_i) = -M_0\, g\, c_i\, \gamma_i + (-1)^{n+l+1}(b\, F_{i-1,i} + b\, F_{i,i+1}). \tag{14}$$

If all forces $F_{i,i+1}$ are prescribed and the geometrical structure, that is, the l_i's and the c_i's are known, equation (14) gives n equations, quadratic in $\bar{\phi}_i$, from which the values $\bar{\phi}_i$ can be determined. Thus, given the initial position of the extremity, we may roughly determine final position after the time $\Delta t = v/l$.

It may be more interesting, perhaps, to reverse the problem and, considering all the $\bar{\phi}_i$ as given, to determine the geometrical structure which minimizes the sum of all the muscular forces that are necessary to produce a given displacement $\bar{\phi}_i$.

For $i = 1$, equation (9) gives

$$b F_{12} = (-1)^{n+2} (A_1 + B_1). \tag{15}$$

Substituting that into equation (9) (with $i = 2$) we find

$$b F_{23} = (-1)^{n+3} (A_1 + A_2 + B_1 + B_2). \tag{16}$$

By substituting this into the equation (9) with $i = 3$, we obtain an expression for $b F_{34}$, and thus by successive steps we obtain in general:

$$b F_{i,i+1} = (-1)^{n+i+1} (A_1 + A_2 + \cdots A_i + B_1 + B_2 + \cdots + B_i), \tag{17}$$

and finally

$$b F = (-1)^{n+1} (A_1 + \cdots + A_n + B_1 + \cdots + B_n). \tag{18}$$

The geometric sum of all the torques is readily obtained from equations (17) and (18) and is found to be,

$$\Sigma b F_{i,i+1} = -\tfrac{1}{2} \Sigma (-1)^n [(-1)^n + (-1)^i] (A_i + B_i). \tag{19}$$

It is, however, the sum of the absolute values of all the torques $b F_{i,i+1}$ that is of more interest, since it is the latter that determines the size of the necessary muscles. It is equal to

$$\begin{aligned} b F_A = \Sigma |b F_{i,i+1}| = n(A_1 + B_1) + \\ (n-1)(A_2 + B_2) + \cdots (A_n + B_n). \end{aligned} \tag{20}$$

With the assumptions which we made and which lead to the approximate equality (2), the A_i's are quadratic forms in the l_k:

$$\Sigma f_{ik} l_i l_k, \tag{21}$$

with

$$f_{ik} = (\alpha_{ik} \bar{\phi}_i + \beta_{ik} \bar{\phi}^2{}_i). \tag{22}$$

The B_i's are linear in the l_i's. Hence the right side of equation (20) is a general quadratic polynomial in the l_i's with linear terms. We

may ask for values of l_i which make that polynomial a minimum with the condition (10). This for a given n, would give the relative sizes of the different parts of the extremity. The problem reduces essentially to a system of n linear equations in the l_i's, but its general treatment is rather messy for arbitrary n and shall not be given here.

Instead we shall assume that all l_i's are for some reason equal or approximately equal, so that

$$l_i = \frac{l}{n}. \tag{23}$$

Each term of any A_i varies, therefore, as $1/n^2$, and since there are n terms in each A_i, therefore, each A_i varies as $1/n$. The B_i's vary as $1/n$. Denoting by h_i the coefficients of proportionality, so that $A_i + B_i = h_i/n$, we have from equation (20)

$$b F_A = \frac{1}{n} (nh_1 + (n-1) h_2 + \cdots h_n). \tag{24}$$

If h^* is the average of all h_i's we have approximately

$$b F_A = \frac{h^*}{n} (1 + \cdots n) = \frac{(n+1) h^*}{2}. \tag{25}$$

Hence F_A increases indefinitely with increasing n, and from the point of view of the minimum force, an extremity consisting of only two parts is the best.

Let us now consider a different situation, namely, when the extremity is lifted by the flexor muscle to be thrust forward during the "flight phase" of running. Now we may consider as a first approximation the position of the center of gravity of the whole organism as prescribed, and study the movement of the extremity with respect to the center of gravity. In this case we may consider the extremity as having a fixed point P_i at its upper end. Since now the movements of the extremity do not involve the displacement of the mass of the whole organism, we do not need to concentrate the mass M at the upper end and only consider the masses m_i of the individual links. Considering those approximately as homogeneous cylindroids, we may put

$$m_i \propto l_i. \tag{26}$$

We now shall number the links from above downward, the first being thus the uppermost. Further we must remember that the distances l_i are measured from the principal point of the ith link to the joint which lies in the direction of the fixed point (now P_2) of the chain (Fischer, 1893). Therefore now the c_i's will not be even approxi-

mately equal to the corresponding l_i's. If all l_i's are equal and if equation (26) holds, then c_i decreases with increasing i. For any l_i's, c_i is proportional to l_i, the coefficient of proportionality being a function of the index i and of all the others l_k $k \leqq i$. The equations of motion of the system are still given by equation (9), but in the expression for A_i and B_i we must substitute for M_0 the value

$$m_0 = \sum m_i . \tag{27}$$

Because of the proportionality of the c_i's to the l_i's, the expression for A_i reduces again to quadratic form in $l_i l_k$ of the same type as before. The only difference now is that bF is applied to the 1st link and not to the nth. In the same manner as before we now find:

$$b F'_A = A_1 + B_1 + 2(A_2 + B_2) + \cdots n(A_n + B_n), \tag{28}$$

and we see, that again for equal l_i's, F_A increases with n.

There is, however, one case in which the situation changes. It is clear that if most of the weight of the extremity is located in the upper part, it will take less work to lift the extremity during the flight phase. Such a distribution of masses is actually the case. Let us, therefore, consider the following case. Let all the links except the most proximal be geometrically similar, so that their mass would vary as l_i^3. The thickness of the link may then be determined by considerations of bending strength of a rod of given length. If we now increase n, keeping m_0 constant, we shall have a shift of the center of gravity of the whole extremity in the proximal direction. The upper link will be much thicker than the other. With increasing n, therefore, all H_i's will shift in the proximal direction, and therefore the c_i's will not remain proportional to the l_i's, but decrease more rapidly. For equal l_i's every term in A_i will now decrease more rapidly than $1/n^2$, and the whole A_i will decrease more rapidly than $1/n$. If, as a very rough approximation, we put now $c_i \propto l_i^2$, then $A_i \sim 1/n^2$. The B_i's also vary as $1/n^2$. The expression for F'_A now becomes approximately of the form

$$bF'_A = h' \frac{n(n+1)}{2n^2} = \frac{h'}{2} + \frac{h'}{2n}, \tag{29}$$

where h' is the average value of the coefficients of $1/n$ in the different $A_i + B_i$. Thus in this case F'_A decreases with increasing n.

For the repelling action of the extremity, when we again have equation (2), the old result holds, namely that F_A increases with n. Hence, denoting by C a constant

$$bF_T = b(F_A + F'_A) = C + h^* n + \frac{h'}{2n}. \tag{30}$$

Hence bF_τ has a minimum for

$$n = \sqrt{\frac{h'}{2h^*}}. \tag{31}$$

The value of h^* is approximately

$$h^* \sim M_0[v^2(\alpha_{ik}\bar{\phi}_i + \beta_{ik}\bar{\phi}_i^2) + g\gamma l], \tag{32}$$

while

$$h' \sim M_0 l[v^2(\alpha_{ik}\bar{\phi}_i + \beta_{ik}\bar{\phi}_i^2) + g\gamma l]. \tag{33}$$

If for the repelling action of the leg and for its lifting during the flight phase the average values $\overline{\alpha_{ik}\bar{\phi}_i + \beta_{ik}\bar{\phi}_i^2}$ are approximately the same, then

$$n = \sqrt{\frac{m_0 l}{M_0}}. \tag{34}$$

With $m_0/M_0 \sim 10^{-1}$ and $l \sim 10^2$ cm, n is about 3. But for shorter extremities it would be less than one, hence only 2 links would exist. Thus while these considerations lead us to the determination of the optimum number of links of an extremity, they have only a theoretical value, for in reality, obviously, that number is determined in some other way.

It must be remembered that unless we make some rather artificial assumptions about the attachments of the muscles, we should consider in equation (29) b itself as variable, namely put $b = kl_i = kl/n$, k being a constant. The forces F_{ik} and therefore F'_A also is likely to vary as $b^2 = k^2l^2/n^2$, being of the form fb^2, where f is essentially the same constant as used in our previous paper (Rashevsky, 1944, p. 28). The constant f is determined by the physicochemical considerations of the properties of the muscles and is probably one of the determining parameters of the species. Putting in equation (30) $b = kl/n$; $F'_A = fk^2l^2/n^2$, we obtain a fourth degree equation for the determination of n. If this equation has more than one real positive root, the smallest must be chosen by the principle of maximum simplicity (Rashevsky, 1943). It is worth while to investigate, what values for n are found in this way.

The reason for having usually three principal members in quadruped extremities may be also an almost kinematic one. For a repelling action two members are enough; however, if there are only two members (Fig. 4a), then the following happens during the "unfolding" of the extremity. While the second member rotates clockwise by an angle $d\phi_2$, the first member rotates counterclockwise by an

FIGURE 4

angle $d\phi_1$. Both rotations tend to lift the body, but while the rotation of 2 moves the body to the right (forward), the corresponding rotation of 1 moves it to the left (backwards). As we have seen (Rashevsky, 1944) in fast running, the body must acquire a velocity, which forms a rather small angle with the horizontal, due to the repelling action of the extremity. Hence the horizontal component of the velocity imparted to the body must be much larger than the vertical component. This will not be the case for an extremity consisting of only two members. With three members (Figure 4b) the situation is different, for now *two* members rotate clockwise, and *one* counterclockwise, increasing the horizontal component. With four members we again have the same situation as with two.

For walking, which does not require much folding of the extremity, and where the extremity rotates in the hip almost as a whole, except for a slight bending in the knee to reduce the lift of the center of gravity, two members may be sufficient. Elephants with very short metatarsus do not run, but walk rapidly in a rather rigid fashion (Howell, 1944).

The mathematical treatment of this aspect of the problem would be as follows: Equation (14) should be solved for given F_{ik}'s and prescribed l_i's for the n average displacements $\bar{\phi}_i$, which in general will be of different signs. If the $\bar{\phi}_i$'s, as well as the initial values of ϕ_i's, are known then the horizontal displacement of the uppermost point of the extremity is also known. Thus we may calculate whether it is larger for $n = 3$, than for $n = 2$, and, if so, how much.

We may consider the ratio of the total kinetic energy T to the kinetic energy T_r of the rotation with respect to the center of gravity, and investigate for what geometrical structure of the extremity that ratio has a maximum. If we consider that $n = 3$ is the optimum from the above kinematic considerations, then we may determine l_1, l_2 and l_3 for a given l from considerations of the minimum of T_r. The expression for T_r is (Fischer, 1893, p. 32):

$$T_r = \frac{1}{2} m_0 [k_1^2 \dot{\phi}_1^2 + k_2^2 \dot{\phi}_2^2 + k_3^3 \dot{\phi}_3^2 + 2d_1 c_2 \cos(\phi_1 - \phi_2) \dot{\phi}_1 \dot{\phi}_2 + 2d_1 c_3 \cos(\phi_1 - \phi_3) \dot{\phi}_1 \dot{\phi}_3 + 2d_2 c_3 \cos(\phi_2 - \phi_3) \dot{\phi}_2 \dot{\phi}_3] ; \tag{35}$$

and for $T_0 = T - T_r$ (Fischer, 1893, p. 35):

$$T_0 = \frac{1}{2} m_0 [c_1^2 \dot{\phi}_1^2 + c_2^2 \dot{\phi}_2^2 + c_3^2 \dot{\phi}_3^2 + 2c_1 c_2 \cos(\phi_1 - \phi_2) \dot{\phi}_1 \dot{\phi}_2 + 2c_1 c_3 \cos(\phi_1 - \phi_3) \dot{\phi}_1 \dot{\phi}_3 + 2c_2 c_3 \cos(\phi_2 - \phi_3) \dot{\phi}_1 \dot{\phi}_3]. \quad (36)$$

The quantity k_i is the radius of inertia of the ith reduced system with respect to H_i. If the values of $\dot{\phi}_i$, correspondingly of $\bar{\phi}_i v/l$, are prescribed, then the problem is to minimize a quadratic form in l_i's, respectively in the c_i's. This problem reduces to a set of the linear equations. We may investigate whether for all $\dot{\phi}_i$ equal we have all l_i or all c_i equal, while a larger $\dot{\phi}_i$ corresponds to a shorter l_i or c_i. If such were the case, it may account for a shorter metatarsal part in plantigrade animals, since that part would have to be moved through a larger angle during extention.

In all cases the solutions will depend on v and l as parameters.

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LITERATURE

Fischer, O. 1893. "Die Arbeit der Muskeln and die Lebendige Kraft des Menschlichen Korpers." *Abh. d. Math. Phys. Klasse d. Königl. Sachsischen Gesellschaft, d. Wissenschaften*, 20, 1–83.

Howell, A. B. 1944. *Speed in Animals—Specialization for Running and Leaping.* Chicago: The University of Chicago Press.

Rashevsky, N. 1943. "Outline of a New Mathematical Approach to General Biology: I." *Bull. Math. Biophysics*, 5, 33–47.

Rashevsky, N. 1944. "General Theory of Quadruped Locomotion." *Bull. Math. Biophysics*, 6, 17–32.

Winkelmann, M. and R. Grammel. 1927. "Systeme Starrer Korper." *Scheel-Geigers Handbuch der Physik*, Vol. 5, pp. 459–483. Berlin: J. Springer.

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TREE TRUNKS AND BRANCHES AS OPTIMUM MECHANICAL SUPPORTS OF THE CROWN: II. THE BRANCHES

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Using assumptions made in a previous paper, a theory of the shapes of primary branches is developed. Two cases are studied: a primary branch which has a portion denuded of secondary branches, and a primary branch with a continuous load of secondary branches. The first case leads to hyperelliptic integrals, the second———to polynomials of second degree.

Denuded stem. We consider a branch as described in the introduction to a previous paper (Esser, 1946; hereafter referred to as Part I). The same notation will be used. The shape of its stem is determined by equation (4) of Part I. The first two terms of the right side of this equation have a ratio of the order of

$$\frac{\cos\theta\, r(z)}{\sin\theta(\zeta - z)}.$$

When θ is not small, this ratio is small and we can therefore disregard the first term of the right side of equation (4) of Part I. Similarly,

$$\frac{G\cos\theta\, r(z)}{\pi\sigma}$$

can be neglected in comparison to

$$\frac{4G}{\pi\sigma}(Y - z\sin\theta).$$

Finally, we neglect also the action of wind. Equation (4) of Part I thus reduces to

$$r^3(z) = \frac{4\omega\sin\theta}{\sigma}\int_z^l (\zeta - z)r^2(\zeta)\,d\zeta + \frac{4G}{\pi\sigma}(Y - z\sin\theta). \qquad (1)$$

Equation (1) determines r as a function of z.

We introduce the following notations:

$$A=\frac{4\,\omega\sin\theta}{\sigma},\quad B=\frac{4\,G\sin\theta}{\pi\,\sigma},\quad X=\frac{Y}{\sin\theta},\quad y(z)=r^3(z). \tag{2}$$

Then equation (1) becomes

$$y(z)=A\int_z^l(\zeta-z)y^{2/3}(\zeta)\,d\zeta+B(X-z). \tag{3}$$

Two successive differentiations give

$$\begin{aligned}\frac{dy}{dz}&=-A\int_z^l y^{2/3}(\zeta)\,d\zeta-B,\\ \frac{d^2y}{dz^2}&=Ay^{2/3}(z).\end{aligned} \tag{4}$$

We consider $y'=dy/dz$ as a function of y, and obtain from the preceding equation

$$\frac{d^2y}{dz^2}=\frac{dy}{dz}\frac{d}{dy}\frac{dy}{dz}=y'\frac{d}{dy}y'=Ay^{2/3},$$

$$d(y')^2=2Ay^{2/3}dy.$$

Integrating and denoting by a the constant of integration

$$y'^2=\frac{6}{5}Ay^{5/3}+a. \tag{5}$$

From physical considerations it follows that the function $r(z)$ is decreasing; therefore y' is negative. The preceding equation gives then

$$\frac{-dy}{\sqrt{\frac{6}{5}Ay^{5/3}+a}}=dz.$$

Integrating and denoting by b a constant of integration:

$$b-\int_{r^3(l)}^{y}\frac{d\zeta}{\sqrt{\frac{6}{5}A\,\zeta^{5/3}+a}}=z. \tag{6}$$

We now determine the two constants of integration. Denote by ρ the radius of the cross-section where $z=l$. We have from equation (1):

$$\rho=r(l)=\sqrt[3]{\frac{4\,G}{\pi\,\sigma}(Y-l\sin\theta)},$$

and from equation (4) we have

$$y'(l) = -B\,,$$

from equation (5) we have

$$a = B^2 - \frac{6}{5} A y^{5/3}(l) = B^2 - \frac{6}{5} A \rho^5\,; \tag{7}$$

and we find $b = l$ by making $z = l$ in equation (6).

Thus we find

$$z = l - \int_{\rho^3}^{y} \frac{d\zeta}{\sqrt{\frac{6}{5} A (\zeta^{5/3} - \rho^5) + B^2}} = l - \int_{\rho}^{r} \frac{3 s^2 \, d s}{\sqrt{\frac{6}{5} A (s^5 - \rho^5) + B^2}}.$$

Hence we obtain, as a final result, the following relation between r and z:

$$z = l - \int_{\rho}^{r} \frac{s^2 \, ds}{\sqrt{\frac{2}{15} A (s^5 - \rho^5) + \frac{B^2}{9}}}, \tag{8}$$

where

$$\rho = \sqrt[3]{\frac{4\,G}{\pi\,\sigma}\,(Y - l \sin\theta)}\,, \quad A = \frac{4\,\omega \sin\theta}{\sigma}, \quad B = \frac{4\,G \sin\theta}{\pi\,\sigma}.$$

Weight of branch. We will now find a simple expression for the weight M_B of the branch. This expression will be used in a subsequent study.

We have

$$M_B = \omega\,\pi \int_0^l r^2(\zeta)\, d\zeta + G\,. \tag{9}$$

A combination of equations (4) and (5) gives

$$\int_0^l r^2(\zeta)\, d\zeta = \frac{-y'(0) - B}{A} = \frac{\sqrt{\frac{6}{5} A y^{5/3}(0) + a} - B}{A}.$$

From equation (7) and from the last equation (2), we find

$$\int r^2(\zeta)\, d\zeta = \sqrt{\frac{6}{5A} [r^5(0) - r^5(l)] + \frac{B^2}{A^2}} - \frac{B}{A}.$$

Substituting this value into equation (9) and using equation (2), we obtain the final result

$$M_B = \sqrt{\frac{3\pi^2 \omega \sigma}{10 \sin\theta}\,[r^5(0) - r^5(l)] + G^2}. \tag{10}$$

We shall now study the particular case where $G = 0$. This case has already been commented on at the end of Part I. Equation (8) reduces to

$$\begin{aligned} z &= l - \int_0^r \frac{s^2\,ds}{\sqrt{\frac{2}{15}As^5}} = l - \sqrt{\frac{15}{2A}}\,2\sqrt{r}, \\ r(z) &= \frac{A}{30}(l-z)^2 = \frac{2\omega \sin\theta}{15\sigma}(l-z)^2. \end{aligned} \tag{11}$$

Substitution of this value into either equation (9) or (10) gives

$$M_B = \frac{4\pi\omega^3 \sin^2\theta}{1125\,\sigma^2} l^5. \tag{12}$$

The interest of this formula is to show that, in our approximation, the weight of a branch varies as the fifth power of its length.

Continuously loaded stem. Instead of considering a primary branch as consisting of a stem terminated by a crown, we now consider a primary branch to consist of a stem loaded with a continuous distribution of secondary branches. Let $\rho(z)$ be the load per unit length of stem in the neighborhood of z. Then the weight of the portion of primary branch (stem plus its load of secondary branches) between the cross-sections z and $z + \Delta z$ is

$$\omega\pi \int_z^{z+\Delta z} r^2(\zeta)\,d\zeta + \int_z^{z+\Delta z} \rho(\zeta)\,d\zeta.$$

The integral equation determining $r(z)$ and corresponding to equation (1) of the preceding problem is now

$$r^3(z) = \frac{4\sin\theta}{\sigma} \int_z^l (\zeta - z)\left[\omega r^2(\zeta) + \frac{\rho(\zeta)}{\pi}\right] d\zeta. \tag{13}$$

Two differentiations give:

$$\frac{d^2 r^3(z)}{dz^2} = \frac{4\sin\theta}{\sigma}\left[\omega r^2(z) + \frac{\rho(z)}{\pi}\right].$$

We will solve equation (13) in one particular case, namely the case where the following four assumptions hold.

I. The length of the secondary branches decreases to zero when we approach the tip of the primary branch. We shall consider a linear decrease, the length $l_2(z)$ of the secondary branch attached at the point z of the primary branch being given by $l_2(z) \propto (l-z)$.

II. The number of secondary branches increases as we approach the tip of the primary branch. We shall consider

$$n(z) \propto \frac{1}{l-z},$$

where $n(z)$ is the number of secondary branches per unit length of primary stem in the neighborhood of z.

III. The weight of the secondary branches is proportional to the fifth power of their length, as in equation (12),

$$M_2(z) \propto l_2^5(z).$$

IV. The secondary branches can be grouped into pairs of branches symmetric relatively to their common point of attachment to the primary stem.

Assumption IV allows us to replace each pair of branches by a weight located at their point of attachment. We obtain from the first three assumptions,

$$\rho(z) = n(z) M_2(z) \propto (l-z)^4,$$
$$\rho(z) = A(l-z)^4,$$

A being some coefficient of proportionality.

Equation (13) now becomes

$$r^3(z) = \frac{4 \sin \theta}{\sigma} \int_z^l (\zeta - z) \left[\omega r^2(\zeta) + \frac{A}{\pi} (l-z)^4 \right] d\zeta.$$

By substitution, we see that this equation has the solution

$$r(z) = a(l-z)^2, \tag{14}$$

where a is the solution of

$$a^3 = \frac{2 \sin \theta}{15\, \sigma} \left[\omega a^2 + \frac{A}{\pi} \right].$$

This equation has one and only one root a. This root is positive. (This result can be seen by making a graph of both members of the equation.)

Equation (14) determines the shape of the primary branch.

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LITERATURE

Esser, M. H. M. 1946. "Tree Trunks and Branches as Optimum Mechanical Supports of the Crown: I. The Trunk." *Bull. Math. Biophysics,* 8, 65–72.

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THE PROBABILISTIC APPROACH TO THE EFFECTS OF RADIATIONS AND VARIABILITY OF SENSITIVITY

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The calculation of the size of the "sensitive volume" or "control center" in biological effects of radiations is discussed from the viewpoint of the probabilistic theory of these phenomena based on the concept of random "effective events." On the bases of that theory, the resistivity of a microorganism to radiation is defined as its "mean life" under a radiation of one roentgen per minute. This mean is calculated for processes with and without recovery. The case of variable sensitivity, as it occurs for instance during mitosis, is discussed in detail. Methods are given to calculate this variability from survival curves or similar experimental data. The theory is applied to experiments of A. Zuppinger on irradiation of *Ascaris* eggs with X-rays.

1. *The physicochemical background of the theory.* The mechanism of biological effects of radiations is complex. In the field of X-rays it is agreed that one of the primary effects of radiation is the ionization which is produced either directly by the radiation quanta or indirectly by the electrons ejected from the atoms. This ionization is in general only a first step in a chain of phenomena leading to the observed effect and consisting in general of some stable chemical change (See e. g. Clark, 1940, chapters iv, viii, x, xi; Clark, 1944; Failla, 1936). Such a change involves, according to the present conceptions, some vital control centers of the microorganism. A center of this kind may consist of a very small aggregate of molecules, or of a single molecule and perhaps even of an aggregate of atoms inside a molecule. As P. S. Henshaw (1944) points out the functional activity of a cell involves a relatively large reserve of material, which, if damaged by radiation, may be renewed more easily than those substances on which the control activity of the cell is based. These latter substances are in general present in much smaller amounts, and it is more difficult to restore them to their original condition once they were inactivated; besides this, their action seems to be dependent to a high degree on their concentration, so that even changes involving small amounts may produce substantial effects. These and other theoretical reasons based on a mathematical analysis of experimental data (Opatowski, 1945b, pp. 162–163) suggest that biological effects of ra-

diation may have a primary relation to the changes occurring in an extremely small part of the microorganism.

The theory of the biological effects of radiations has been limited up to now to a probabilistic approach to these primary processes consisting of *ionizations* and dependent directly on the random absorptions of radiation quanta by the *control centers* or *sensitive volumes* of the organism. However it must be kept in mind that what actually is observed is an *effect of the ionization.* This effect may be reached in three different ways: (i) through some action which is developed practically instantaneously; (ii) through a chemical or biochemical reaction, and therefore through a process of a deterministic character requiring a certain time after the absorption of the radiation quanta occurred; (iii) through a combined action of both mechanisms. The latter is the most general type of process involving a superposition of random and deterministic phenomena. A mathematical analysis of some experimental data suggests that this general mechanism may actually occur. The second process representing the so-called delayed action is substantially identical with the first, since it involves only a translation of the origin of the time axis. The present theory, as well as those previously published, concern the first two mechanisms. These theories are based on the concept of an *effective event* occurring in a sensitive volume or control center of the microorganism. Such an event may be the absorption of a photon or an ionization; it may cause the formation of a new substance inside the sensitive volume and elsewhere, or may change other physical characteristics of the cell leading to such phenomena as cell swelling, variations in concentrations and in rates of metabolism, etc. In the mathematical theory the occurrence of an effective event in the sensitive volume is considered as a *transition* of that volume to a new *state.* The observed effect is reached after a certain number of transitions between the successive states has been carried out, so as to reach a state n which represents the observed effect (cf. Opatowski, 1942; 1945b; 1946). The probabilistic model used (Markoff chains) has been defined in a previous paper (Opatowski, 1946). It is the same model which has been introduced by E. Rutherford into the field of radioactive transformations, except that we consider here also the possibility of reverse transformations representing the phenomenon of recovery. The recovery may be due to reversibility of reactions, to occurrence of new reaction chains or to ionic recombinations. The states are numbered progressively $0, 1, \cdots, n$. During an infinitesimal interval of time dt transitions between two consecutive states are considered as the only possible, which is a limitation of the theory. The probability of a transition $(i—1 \rightarrow i)$ within an interval

of time $(t \cdots t+dt)$, under the hypothesis that at the time t the state i—1 existed, is assumed to be $k_i dt$, where k_i is not necessarily a constant. A similar probability for the transition $(i+1 \rightarrow i)$ is put equal to $g_i dt$. Under these assumptions the probability $Y_n(t)$ that the microorganism reaches the state n at a time t of irradiation of a sample of microorganisms has been calculated (Opatowski, 1942, 1945, 1946). The function $Y_n(t)$ is the *global transition probability*, inasmuch as it represests the probability of transition from the initial state to the state which is under observation. (A similar probabilistic model has been suggested recently also for the action of viri and antibodies [see Jordan (1941); v. Schelling (1942); Koyenuma (1942)].

From a formal viewpoint the theory may be interpreted as representing a kinetics of a chain of reactions, which in general may be reversible. However, the interpretation based on the concept of random effective events gives a possibility of *calculation of the size of the sensitive volume*. For this purpose the effective events are interpreted as absorption of photons or formation of ions. For instance, in the case of X-rays, the calculation is based on the assumption that the energy absorbed by the irradiated sample is measured in roentgens. This measurement gives that fraction of the total radiation energy E which would be absorbed in ionizing 1 cm^3 of air. Consequently the number of ions produced in 1 cm^3 of air by the energy E may be calculated from the definition of the roentgen (2.1×10^9 ion pairs per roentgen in 1 cm^3 of air (cf. Clark, 1940, p. 192). The number of ions produced is proportional to the absorption coefficient; this enables us to calculate the number n_1 of ions produced by E in 1 cm^3 of irradiated matter, as soon as the chemical composition of the latter is known. A comparison of the experimental results with the mathematical expression of the probability function $Y_n(t)$ gives the number of effective events n produced in the sensitive volume by the energy E. Let ν be the number of ions in the sensitive volume corresponding to one effective event. Then $\nu n/n_1$ is *the size of the sensitive volume*. At the present stage of our knowledge of the action of X-rays, only a range of values may be assigned to ν; consequently what the above calculation gives is only *a lower and an upper limit for the size of the sensitive volume*. This fact does not seem to have been noticed by some authors. If formation of each ion, indifferently of its sign, is an effective event, then $\nu = 1$. If ions of a certain sign count only for the biological effect, then $\nu = 2$. If collisions of the primary photons with the sensitive volume are the only effective events, then ν may be very large within wide limits, since an electron of 50,000 eV may produce 1,000 ions, whereas one of 2,000,000 eV may produce more than 100,000 ions. Comparative experiments with

different wave lengths could perhaps give some information as to the nature of the quantity ν.

It should be, however, kept in mind that the above method of calculation of the sensitive volume is based on several approximations: First of all, the irradiated microorganisms are physically nonhomogeneous, even if they form a biologically homogeneous aggregate. The X-ray beam, even if monochromatic at the source, may become polychromatic inside the living matter. The formation of ions along the electronic track is not uniform, being more dense at its end, because of lower electron velocities. Elements of higher atomic number are loci of intense ionization, since the absorption coefficient increases rapidly with the atomic number. The fact that these elements form only a very small fraction of the irradiated matter does not preclude their possible importance for the final effect. In fact, it is well known how essential small amounts of impurities are for certain photochemical phenomena (cf. e. g. Hill, 1946; Noddack, 1926, p. 605). A theory which would take into account all these facts would be complicated, although some attempts in this direction have already been made, for instance, the theory of R. Glocker, (1932) which does not neglect the possibility that an ionization of the sensitive volume may be due to an absorption of a radiation quantum outside of that volume. In order to consider the possibility of occurrence of a primary effective event outside of the sensitive volume, some authors suggested recently the concept of a *physically sensitive volume* to be distinguished from the actual biological sensitive volume (Möglich, Rompe and Timoféeff–Ressovsky, 1942). However, as far as the ionization is concerned, this possibility was already taken into account in a quantitative manner in the theory of R. Glocker.

The physicochemical background of the theory of biological effects of radiations has been outlined here in a very concise manner; for more detail the reader is referred to the literature already quoted as well as to the following publications in the field of X-rays and their applications: Compton–Allison, 1935, chapter vii and pp. 5–18; Mayneord, 1938, 1940; Kirchner, 1930; Gray, 1936; Victoreen, 1944; Behnken, 1926; Lauritsen, 1933; Webster, 1933; Condon–Terrill, 1927; Glocker, Hayer and Jüngling, 1929; Scott, 1937; Braun and Holthusen, 1929; Grebe, 1926; Rump, 1927, p. 290.

2. *The object of the paper.* In certain cases the sensitivity of the organism to the radiation is variable. This occurs particularly during mitosis, and must be taken into account when the duration of the irradiation is of the same order of magnitude as the life cycle of the microorganism. An increase of the sensitivity to radiation may

appear in two different forms: (i) The number of effective events necessary to obtain a certain effect may decrease; (ii) the probability of occurrence of an effective event may increase for instance because of an increase of the sensitive volume. In the first case the number n changes, in the second case the quantities k_i, g_i which express the probabilities of transition from one state to another change. The first case does not present any mathematical problem: it just means that at certain moments the number n changes by 1, that is, that the global transition probability $Y_n(t)$ has a finite jump at that moment. The second case means that k_i and g_i are functions of the time. We consider this case in detail, mainly under the assumption that no recovery occurs ($g_i = 0$). The theory has as its objective the determination of the functions $k_i(t)$ from experimental values of $Y_n(t)$. Such determination is carried out explicitly under the assumption that all the k_i's are equal to each other; this involves either the approximation of taking for the k_i's a suitable average value k, or the assumption that an inactivation of only a small part of the sensitive volume is sufficient to produce the observed effect. The actual calculation of the function $k(t)$ involves a first trial computation on the basis of an arbitrarily chosen value of n, which is then improved to the correct value. The theory indicates the type of experiments which are necessary for the calculations. The computations, which involve the use of the *incomplete gamma function*, are applied to a set of experiments on irradiation of *Ascaris eggs* with X-rays.

A new mathematical formulation of the *resistance of a microorganism to irradiation* is introduced. It is based on the concept of *average duration of global transition*, i. e., of the average time necessary for the transition ($0 \to n$). Such time L represents the *average life* of the microorganism in the case in which the state n represents its death. In the case in which the intensity of radiation is 1 roentgen/min, L is measured in roentgen and is defined as the *resistivity of the microorganism*. General expressions for the calculation of L are given and explicit formulae are obtained in the cases in which the k_i's and g_i's are independent of i.

3. *The average duration of global transition (the mean life).* We consider here only the cases in which the *n*th *state is final*, that is, $k_{n+1} = 0$.

(i) We discuss first three types of processes in which the *transition intensities* k_i *and* g_i *are independent of the time* t.

(*a*) Consider the case in which *no recovery occurs, that is, the intensities* g_i *of all reverse transitions are zero.* Then $Y_n(t)$ is a

monotonically increasing function from 0 to 1 with $Y_n(\infty) = 1$ (Opatowski, 1942, pp. 84, 87). The mean life of a microorganism between the states 0 and n is defined as the mathematical expectation of t:

$$L = \int_0^1 t\, dY_n = \int_0^\infty t\, Y'_n(t)\, dt\,. \tag{1}$$

Deterministically this definition is intuitive, because dY_n is the fraction of the total number of microorganisms which reach the state n between t and $t + dt$, i. e., which "live" a time t. (The concept of average life or of average duration of transition between the states 0 and n is analogous to the concept of mean life of an atom in a quantum state in theoretical physics, (e. g. Richtmyer and Kennard, 1942, pp. 304–305). From a formula concerning the moments of the function $Y'_n(t)$ (Opatowski, 1942, p. 87) we have

$$L = \sum_{i=1}^{i=n} 1/k_i = n/k\,, \tag{2}$$

where k is the harmonic average of all the k_i's.

(*b*) Consider now the case in which the *reverse transitions occur between intermediate states only, that is, a process in which all the* k_i's *and* g_i's *are different from zero,* except $k_{n+1} = g_{n-1} = 0$. It is known (Opatowski, 1945b, pp. 170–174) that such a process is equivalent to a process consisting of direct transitions only between the same number of states with suitable transition intensities $\bar{k}_1, \cdots, \bar{k}_n$, n being a final state also in this new process. The quantities $-\bar{k}_i$ are the n roots of the equation in s:

$$||a_{r,c}||_n = 0\,, \tag{3}$$

where

$$\begin{aligned} &a_{r,r} = s + k_{r+1} + g_{r-1};\ a_{r,r-1} = k_r;\quad a_{r,r+1} = g_r;\\ &a_{r,c} = 0 \text{ for } |r - c| > 1;\\ &0 \leqq r,c \leqq n - 1\,. \end{aligned} \tag{4}$$

Consequently $L = \sum_{i=1}^{i=n} 1/\bar{k}_i$. But (Opatowski, 1945b equation 28):

$$k_1\, k_2 \cdots k_n = \bar{k}_1\, \bar{k}_2 \cdots \bar{k}_n;$$

therefore

$$L = a_{n-1}/(k_1\, k_2 \cdots k_n)\,, \tag{5}$$

where $a_{n-1} = \sum \bar{k}_1\, \bar{k}_2 \cdots$ is the elementary symmetric function of degree n—1 of the $\bar{k}_i$'s, that is, a_{n-1} is the coefficient of s in equation (3). Consequently (cf. Opatowski, 1945b, equations 15 and 16) a_{n-1} is the

sum of all the minors of order $n-1$ of the determinant (3) (4) calculated for $s = 0$.

Consider as an example the case in which the k_i's and g_i's are independent of i, that is:

$$k_i = k\,(1 \leqq i \leqq n)\,; \quad g_i = g\,(0 \leqq i \leqq n-2).$$

Then, the following explicit form of the equation (3) (4) may be used (Opatowski, 1945a, equations (17), (6) :

$$E_n - g\,E_{n-1} = 0\,, \tag{6}$$

where E_n equals $(kg)^{n/2}$ multiplied by a Tchebychev polynomial in

$$\sigma = (s + k + g)/(2\sqrt{kg}),$$

that is,

$$E_n = (kg)^{n/2}[(\sigma + \sqrt{\sigma^2 - 1})^{n+1} - (\sigma - \sqrt{\sigma^2 - 1})^{n+1}]/(2\sqrt{\sigma^2 - 1}). \tag{7}$$

The coefficient of s in the expansion of E_n is easily calculated as

$$(dE_n/ds)_{s=0} = k^{n-1}(1-r)^{-2}[(n+1)(1+r^{n+1}) - (1+r)(1-r)^{-1}(1-r^{n+1})], \tag{8}$$

where $r = g/k$. Consequently, a_{n-1}, the coefficient of s in equation (6) is:

$$k^{n-1}(1-r)^{-2}[n - (n+1)r + r^{n+1}]$$

and from equation (5) we obtain the average life:

$$L = [n - (n+1)\,r + r^{n+1}]/[k(1-r)^2] = (n/k)\,[1 + (1 - n^{-1})r + \cdots]. \tag{9}$$

If $r = 0$ this expression reduces to (2). *If there is recovery, the average life increases, in a first approximation, proportionally to the ratio* r *of the intensities of direct and reverse transitions.*

(*c*) Consider now a process (*p*) in which the n*th state is final and a reverse transition from the* n*th state is possible,* that is, $k_{n+1} = 0$, $g_{n-1} \neq 0$. As usual, let $Y_n(t)$ be the global transition probability for this process. Consider the equation

$$||a_{r,c}||_{n+1} = 0\,, \qquad 0 \leqq r,c \leqq n\,, \tag{10}$$

where the determinant $||a_{r,c}||$ is defined in the same way as in equation (3), except that its order is now one unit higher. We know (Opatowski, 1945b, pp. 174–175) that the relation (10), considered as an

equation in s has one root equal to zero, and all the remaining roots negative numbers $-\bar{k}_1, -\bar{k}_2, \cdots, -\bar{k}_n$. Let $\bar{Y}_n(t)$ be the global transition probability for a process $(\bar{p})$ consisting of direct transitions only between the contiguous states $0, 1, \cdots, n$ with the intensities respectively $\bar{k}_1, \bar{k}_2, \cdots, \bar{k}_n$. Then (Opatowski, 1945b, pp. 174–175):

$$Y_n(t) = k_1 k_2 \cdots k_n \bar{Y}_n(t) / (\bar{k}_1 \bar{k}_2 \cdots \bar{k}_n). \tag{11}$$

Since $Y_n(\infty) = 1$, we have now (Opatowski, 1945b, p. 776):

$$Y_n(\infty) = k_1 k_2 \cdots k_n / (\bar{k}_1 \bar{k}_2 \cdots \bar{k}_n) < 1,$$

and equation (11) may be written

$$Y_n(t) = Y_n(\infty) \bar{Y}_n(t).$$

To represent the average life, the formula (1) must be modified in the following manner:

$$L = \int_0^{Y_n(\infty)} t dY_n / Y_n(\infty) = \int_0^1 t d\bar{Y}_n.$$

We see in this way that *the average life in the processes* (p) *and* $(\bar{p})$ *is the same.* Therefore:

$$L = \sum_{i=1}^{i=n} 1/\bar{k}_i. \tag{12}$$

If we divide the determinant (10) by s, we obtain a polynomial:

$$R = b_n + a_{n-1} s + \cdots + s^n,$$

and by known properties of the elementary symmetric functions of zeros of polynomials we have from equation (12)

$$L = a_{n-1}/b_n.$$

As an example consider again the case in which the k_i's and g_i's are independent of i, that is,

$$k_i = k (1 \leqq i \leqq n); \qquad g_i = g (0 \leqq i \leqq n-1).$$

Then (Opatowski, 1945a, formula 5): $R = E_n$. Consequently a_{n-1} equals the expression (8) and b_n is the value of the expression (7) for $s = 0$:

$$b_n = k^n (1 - r^{n+1}) / (1-r).$$

We obtain in this way:

$$L = [(n+1)(1-r^{n+1})^{-1}(1 + r^{n+1}) - (1-r)^{-1}(1+r)] / [k(1-r)]$$
$$= (n/k)[1 + (1-2n^{-1}) r + \cdots].$$

Also here the recovery increases the average life in a similar manner as in the process (*b*).

(ii) We consider now a case of *variable sensitivity* without recovery, that is, without reverse transitions, so that all g_i's are zero. We assume that the variability of sensitivity is reflected in a *dependence of the* k_i*'s* on the time in the form

$$k_i = K_i f(t), \tag{13}$$

where the K_i's are independent of t. If we introduce a new time variable

$$T = \int f(t)\, dt,$$

we obtain the probability Y_n by taking its expression valid for the case (i*a*) and changing in it formally t into T (Opatowski, 1945b, p. 165; 1942, p. 84). However the calculation of the average life must be made with reference to t as the time variable. This calculation can be carried out explicitly when t is a polynomial in T:

$$t = \sum_m c_m T^m,$$

and if $T \to +\infty$ whenever $t \to +\infty$. Under these assumptions, and choosing $t = 0$ as the lower limit in the integral which defines T, we can write:

$$L = \int_0^1 t\, dY_n = \int_0^\infty t Y'_n(T)\, dT =$$

$$\sum_m c_m \int_0^\infty T^m Y'_n(T)\, dT = \sum_m m!\, c_m\, h_m(K_1^{-1}, \cdots, K_n^{-1}), \tag{14}$$

where $h_m(x_1, \cdots x_n)$ is the *complete homogeneous symmetric function* of the x_i's, that is, the sum of all the possible products of the x_i's of degree m, each of the x_i's being taken any number of times up to m. (These functions are called also homogeneous product sums or alef functions of Wronski.) The passage from the fourth to the fifth member of equation (14) involves the use of a known relation concerning the moments of the function Y'_n (Opatowski, 1942, p. 87).

4. *Determination of the change of sensitivity of the microorganism from experimental data.* Since processes with recovery are reducible to those without recovery (Opatowski, 1945b, pp. 170–177) we may assume the intensities of reverse transitions g_i to be all zero. We consider the intensities of direct transitions $k_i(t)$ to be functions

of the type (13). As already mentioned, the global transition probability $Y_n(t)$ is obtained from the expression of Y_n valid when the k_i's are independent of t, by performing the substitutions:

$$k_i \to K_i; \quad t \to T,$$

where it is convenient to define the new time variable T by the equation

$$T = \int_\tau^t f(t)\,dt. \tag{15}$$

We will identify the time variable t with the *age of the microorganisms,* each of the irradiated samples being assumed to be homogeneous, so that all microorganisms of a sample are of the same age. The quantity τ will be chosen as *the age at the moment when the irradiation of the sample starts,* τ is in general different for each sample. The age is taken here not in an absolute sense, but with reference to the youngest sample considered, $\tau = 0$ being taken as the moment in which the irradiation of that sample starts.

The case which has been treated up to now by various authors is the one in which the K_i's are independent of i. The meaning of this assumption has been discussed in Section 2. This is also the assumption that we consider here. We take $k_{n+1} = 0$, as before, that is, we assume that any change beyond the nth state does not affect the observation (the nth state is the final one). We put $K_i = KJ$ for $i \leqq n$, where K is a constant and J is the intensity of radiation, because we assume that the transition intensity k_i are proportional to J. Then it is known that (cf. e. g. Crowther, 1926):

$$\begin{gathered} Y_n(t) = \gamma(q, n) \text{ where } q = KJT, \\ \gamma(q, n) = \int_0^q [e^{-q} q^{n-1}/(n-1)!]\,dq. \end{gathered} \tag{16}$$

$\gamma(q, n)$ is the *incomplete gamma function.* Using the symbols of K. Pearson's tables (1934) we shall write:

$$Y_n(t) = I(u, p) \text{ where } u = q/\sqrt{n}, \quad p = n-1.$$

Let $Y_e(t)$ represent experimental values of the function $Y_n(t)$. We consider the problem of determining the sensitivity

$$k(t) = KJf(t)$$

from $Y_e(t)$. It will be seen that in order to solve the problem it is necessary to have several sets of values of Y_e, each set corresponding to a different value of τ, that is to a different age of the sample at the moment when the irradiation starts. The various sets of $Y_e(t)$

must correspond to overlapping intervals of time t, that is, each age range must be covered by several samples. Otherwise the problem would have an infinite number of solutions, since n is unknown, and to each value of n corresponds one solution. In fact, the function $Y_e(t)$ is obtained from irradiation experiments, whereas the function $\gamma(q, n)$ is known, for instance through its values tabulated by K. Pearson. For each value of n, the function $q(t)$ is determined by the equation

$$\gamma(q, n) = Y_e(t),$$

which has a unique solution $q = q(t)$. This solution can be obtained through the following numerical procedure; choose an arbitrary value q_1 of q, Pearson's tables give the corresponding value γ_1 of γ for each assigned value of n; the experimental data give a value t_1 of t for which $Y_e(t_1) = \gamma_1$. In this way for each value of q the corresponding value of t is obtained. A numerical or graphical differentiation of $q(t)$ gives then the sensitivity according to the following relation (cf. equations 16 and 15):

$$dq/dt = KJf(t). \tag{17}$$

The use of Pearson's tables could be avoided by the following method, which is very complicated, however: Calculating the expression

$$d \log Y'_e(t)/dt,$$

where $Y'_e(t)$ is taken as $dY_n(t)/dt$ and for $Y_n(t)$ the equations (15) and (16) are used, an integral equation of the type

$$\int_0^t f(t)\,dt = G(f, df/dt) \tag{18}$$

is obtained, where G is a rational fractional function of second degree in f and df/dt. A differentiation of equation (18) with respect to t gives a nonlinear differential equation of second order in $f(t)$. The initial conditions for $f(t)$ are complicated involving values of derivatives of f up to the nth order. However, for our purpose, the numerical method, as previously outlined, is completely sufficient.

Let $\tau = 0$ and $\tau = \tau_1$ be the two smallest values of τ for which experiments are carried out. Consequently the range $0 < t < \tau$, is covered by experiments on one sample only; therefore, the sensitivity calculated in that range may be incorrect because of the arbitrary choice of the value of n. Before we show how this error may be corrected, we have to make some preliminary clarifications. We exclude the possibility of an infinite sensitivity at $t = 0$, because this would mean an instantaneous action of the radiation on the whole sample, which is in contradiction with experimental findings. Consequently,

since our range of time includes $t = 0$, we can expand $f(t)$ in Mac-Laurin series of t, for sufficiently small values of t:

$$f(t) = f_0 + f_1 t + \cdots . \tag{19}$$

We assume that the experiments are pushed down to such a low value of τ, that the series (19) converges for $\tau = \tau_1$. A particular meaning has the case $f_0 = 0$, because it requires that the sensitivity be zero at the beginning of the radiation ($t = 0$) and becomes apparent only as the radiation goes on. We have here a case in which *the sensitivity to radiation is induced by the radiation itself.* There is, of course, still another interpretation of the condition $f_0 = 0$ possible, that is, that the microorganism exhibits a lack of sensitivity for some *intrinsic reason* existing during a certain range of its age. Such a possibility can be cleared by an additional experiment which should start at an age slightly lower than τ_1. We exclude these two possibilities from further consideration, so that we assume $f_0 \neq 0$.

We show now how a possible erroneous determination of $f(t)$ due to arbitrariness in the choice of n may be corrected. The function $f(t)$ *represents the change of sensitivity.* Let $F(t)$ be its expression determined from experimental values of $Y_e(t)$, by assuming a certain value N for the number n of effective events. Since $F(t)$ is not necessarily the correct expression of the change of sensitivity, the expansion of $F(t)$ in power series has a general form

$$F(t) = F_i t^i + F_{i+1} t^{i+1} + \cdots , \tag{20}$$

where i may be any real number, so that even the case $F(0) = \infty$ is not excluded. Let n be the correct number of effective events and $f(t)$ the corresponding correct expression of the change of sensitivity, so that for $f(t)$ the expansion (19) holds with $f_0 \neq 0$. Since the pairs of quantities $[f(t), n]$ and $[F(t), N]$ are derived from the same experimental data, they must satisfy the following relation (cf. equations (15) and (16)):

$$\gamma(q, n) = \gamma(Q, N), \tag{21}$$

where

$$q = KJ \int_0^t f(t)\,dt; \quad Q = KJ \int_0^t F(t)\,dt. \tag{22}$$

The derivative of equation (21) with respect to t gives the relation:

$$e^{-q} q^{n-1} f(t)/(n-1)! = e^{-Q} Q^{N-1} F(t)/(N-1)! \tag{23}$$

Substituting here the expansions (19), (20) and taking into account the relations (22), we obtain for the lowest terms in equation (23):

$$[F_i/(N-1)!][KJF_i/(i+1)]^{N-1} t^{N(i+1)-1} + \ldots =$$
$$[f_0/(n-1)!](KJf_0)^{n-1} t^{n-1} + \cdots .$$

This relation is an identity, therefore:

$$n = N(i+1), \qquad (24)$$

which gives *the correct number* n *of effective events on the basis of a fit of experimental data with any number* N *of events.* This procedure will be illustrated in the following section.

5. *Application of the theory to experimental results.* We apply now the theory to some experimental results on irradiation of *Ascaris* eggs with X-rays. G. Perthes (1904) was the first who observed an effect of X-rays on the process of cellular division in *Ascaris* eggs. N. M. Stevens (1909) carried out similar experiments with ultraviolet light and J. C. Mottram (1913) with beta and gamma rays of radium. The experiments have been repeated by many other authors since then (Holthusen, 1920, 1921; Schleip, 1923; Ruppert, 1924; Dognon, 1926; Zuppinger, 1928; Liechti, 1929; Cook, 1939). The effect has been described as irregularities and prevention of development or change of rate of development. In counting the number of microorganisms which exhibit an effect of radiation, Holthusen (1920) distinguishes two degrees of injury, one in which some form of worm is distinguishable, and the other one, in which the development reaches only a stage of an irregular cluster of cells. Other authors (e.g. Zuppinger) do not differentiate between the degrees of injury in evaluating the effect of radiation. From a theoretical viewpoint both procedures are admissible: the first involves two observable states and consequently two different values n_a and n_b of n; in the second procedure one state only is observed, that one which corresponds to the smaller of the two values n_a, n_b. For an application of the theory outlined in the previous sections the experimental results of A. Zuppinger seem to be more appropriate, because they cover various ages of the microorganisms and are among the most accurate that are available in this field.

Figure 1 shows the results of 6 sets of experiments of A. Zuppinger, each one carried out with a different starting age. Three different intensities of radiation were used from 5.37 to 50 Roentgen/min. The experiment with 50 Roentgen/min. covering the range of t from 0 to 48 minutes was carried out in the earliest stage of development; this is the only experiment which has been discussed theoretically by other authors. By assuming a constant sensitivity k, A. Zuppinger (1928) obtained the closest fit with a number of effective events

$n = 5$; since the fit was not satisfactory he assumed a variability of n due to a non-homogeneity of the sample. The number n was taken according to a Poisson distribution. The expression of the probability $Y_n(t)$ involves then Bessel functions and is much more complicated than in our theory. Nevertheless the fit could be improved only slightly by assuming the most probable value of n equal to 11. Recently N. Koyenuma (1943) obtained a very good fit for the above mentioned single experiment concerning the first 48 minutes after incubation. He did so by introducing an additional assumption, that the microorganism contains several sensitive volumes and that the injury becomes manifest when a certain minimum number of effective events occurs in each of these volumes. His calculations involve series of Bessel functions and the fit is obtained with four sensitive volumes and $n = 6$ as the most probable number of events. Since the reaching of the two–cell stage requires 3 to $3\frac{1}{2}$ hours, whereas the whole experiment lasted 48 minutes it would have to be assumed that each cell contains all of the four sensitive volumes. Neither Zuppinger nor Koyenuma took into account the fact that the *Ascaris* eggs exhibit a strong variability of sensitivity during mitosis, as it has been positively established by Zuppinger himself as well as by C. Mottram (1913), H. Holthusen (1920) and A. Liechti (1929).

The present analysis is not limited to the single experiment considered in the calculations of A. Zuppinger and N. Koyenuma. It is based on several sets of data of A. Zuppinger on continuous irradiation of *Ascaris* eggs which have been conserved in aerobic conditions. Only a few sets of Zuppinger's results were discarded; they concern some preliminary experiments, in which the irradiated samples were kept close to the X-ray tube, without protection against the heat emanated from the tube. [It was found by Zuppinger himself that the heat has a perturbatory effect. A. Dognon (1926) found also that beyond 22°C the sensitivity of *Ascaris* eggs to X-rays increases very rapidly with temperature. H. Holthusen (1920) emphasized also the same fact]. With this exception and with the exclusion of some data concerning special experimental conditions (*Ascaris* kept on ice and eggs in anaerobic conditions) all data of Zuppinger were used.

The process has been assumed to be without recovery, in agreement with the experimental findings of A. Zuppinger and other authors. Zuppinger finds even that fractional irradiation produces more effect than a continuous one with the same amount of energy. Such increase of effect by fractional irradiation has been observed, however, only over periods of days or weeks, and mostly on eggs which have been kept in anaerobiosis. A quite pronounced effect of recovery has been observed by E. V. Cook (1939), but again only over peri-

ods of weeks and exclusively at lower temperatures (5°C). According to Cook the capacity of recovery depends here on the very low metabolic rate due to the low temperature, so that the X-rays produce their full effect long before the cleavage takes place.

In a theoretical analysis of the results of A. Zuppinger it is therefore justified to neglect the recovery and to consider the process as consisting of direct transitions only. The intensities of transition between each two states will be given by expressions of the form of equation (17) as discussed in the previous section. As the first trial

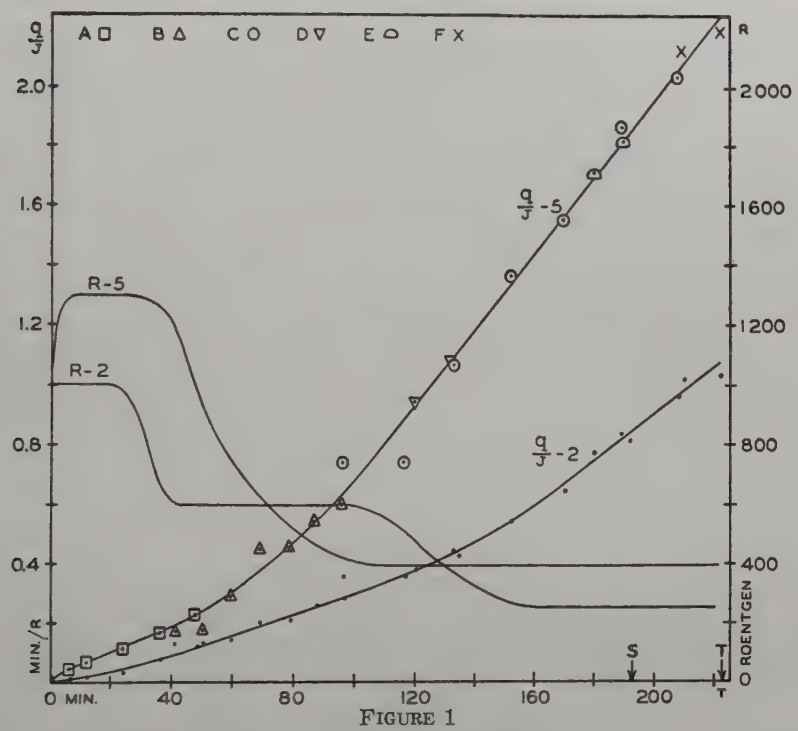

FIGURE 1

Determination of the change of resistivity of Ascaris eggs to X-rays during mitosis. Experiments of A. Zuppinger (1928): sets *A*, *D*, *E*, *F* — intensity 50 R/min., set *B* — 10.86 R/min., set *C* — 5.37 R/min. The experimental data are the same for both curves *q/J* and have common abscissae; for the curve *q/J* — 2 they are indicated with dots only. The interval between *S* and *T* represents the time within which practically the full transition from the single to the two-cell stage is accomplished (90% single cells at *S* and 1% at *T*). For further details, reference is made to the paper by A. Zuppinger (set *A* — p. 663, Fig. 13 right; sets *B* and *C* — p. 677, Fig. 19, 50 and 70.7 cm distance of the sample from the tube; sets *D* to *F* — p. 663, Fig. 13 left). The percentage of eggs injured by causes independent of radiation has been taken into account in the same way as by A. Zuppinger. The large dispersion in the sets *B* and *C* is probably an effect of the heat irradiated from the tube. The curve *R* — 2 represents the *instantaneous resistivity in Roentgen.*

value of the number of effective events we choose the one considered by A. Zuppinger: $n = 5$. From experimental data we calculate q/J as a function of the time t by means of Pearson's tables of the incomplete gamma function. These values are plotted in the diagram in minutes per Roentgen (curve $q/J - 5$). Each of the six experiments leads to a different curve. For convenience of drawing, these curves have been shifted upwards by various amounts, which are immaterial for our conclusions since we are interested only in the slopes of these curves. (These amounts are in R/min: set $A - 0$; set $B - 0.13$ and 0.17; set $C - 0.35$ and 0.74; set $D - 0.38$ and 0.94; set $E - 0.76$ and 1.7; set $F - 1.1$ and 2.08, where the first figures refer to the curve $q/J - 2$ and the second to the curve $q/J - 5$). The differentiation of q/J with respect to the time gives the function $Kf(t)$ according to equation (17). From this the quantity $n/[Kf(t)]$ is calculated. If the sensitivity were constant, $n/(Kf)$ would represent the "average life" of the microorganism in minutes under an irradiation of 1 Roentgen per minute, that is, the *resistivity of the microorganism in Roentgens*. This is a consequence of equations (2) and (13). In the present case, however, $f(t)$ is a function of time. Therefore we will call the quantity $n/(Kf)$ the *instantaneous resistivity* (curves R). It is seen from the diagram that assuming 5 effective events, the resistivity of the microorganism is zero at $t = 0$, that is, its sensitivity is infinite, which is impossible on the basis of the discussion of Section 4. We use the method of that section to correct the number n and consequently to obtain the correct resistivity curve. Using the symbols of Section 4, we have: $N = 5$, and i is determined from the exponent of the lowest term in the expansion

$$q/J = [KF_i/(i+1)]\, t^{i+1} + \cdots , \tag{25}$$

which is obtained from equations (20) and (22). The first term of expansion (25) is fitted to the curve $(q/J - 5)$ between $t = 0$ and $t = 20$. Such a fit is easily done by using the elementary formula

$$i + 1 = t_1\, q'_1/q_1 , \tag{26}$$

where q_1 and q'_1 are the values of q/J and of its time derivative for $t = t_1$, t_1 being in our case any value of t between 0 and 20. These calculations give $i = -0.6$. Consequently from equation (24) we have the *correct number of effective events*: $n = 2$. Now, with $n = 2$ the calculations are carried out in the same way as before with $n = 5$. The results are shown in the diagram as the curves $(q/j - 2)$ and $(R - 2)$. It should be pointed out, that the data available do not make it possible to carry out the calculations very accurately, and the results obtained should be interpreted accordingly. The decrease of re-

sistivity R from 1,000 to about 250 Roentgen during the cellular division is in agreement with the results of C. Mottram (1913), H. Holthusen (1921) and A. Liechti (1929) which estimated an increase of vulnerability of *Ascaris* eggs to X-rays from 2 to 8 times.

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LITERATURE

Behnken, H. 1926. "Röntgentechnik." *Handbuch d. Physik*, **17**, 126–194.

Braun, R. and H. Holthusen. 1929. "Einfluss der Quantengrösse anf die biologische Wirkung verschiedener Röntgenstrahlenqualitäten." *Strahlentherapie*, **34**, 707–734.

Clark, G. L. 1940. *Applied X-Rays*. New York: McGraw-Hill.

Clark, G. L. 1944. "Roentgen Rays: Chemical Effects." Glasser's *Handbook of Medical Physics*, 1345–1348. Chicago: Year Book Publishers.

Compton, A. H. and S. K. Allison. 1935. *X-Rays in Theory and Experiment*. New York.

Condon, E. U. and H. M. Terrill. 1927. "Quantum Phenomena in the Biological Action of X-Rays." *Journal Cancer Res.*, **11**, 324–333.

Cook, E. V. 1939. "Influence of Low Temperature on Recovery from Roentgen Rays." *Radiology*, **32**, 289–293.

Crowther, J. A. 1926. "The Action of X-Rays on Colpidium Colpoda." *Proc. Roy. Soc. London.* **(B)**, **100**, 390–404.

Dognon, A. 1926. "Action de la température sur la radiosensibilité de l'oeuf d'Ascaris." *Compt. Rend. Soc., Biol.*, **94**, 466–468.

Failla, G. 1936. "Ionization and Its Bearing on the Biological Effects of Radiation." Duggar's *Biological Effects of Radiation*, 87–122. New York: McGraw-Hill.

Glocker, R. 1932. "Quantenphysik der Röntgenstrahlenwirkung." *Zeit. f. Physik*, **77**, 653-675.

Glocker, R., E. Hayer, and O. Jüngling. 1929. "Über die biologische Wirkung verschiedener Röntgenstrahlenqualitäten bei Dosierung in R-Einheiten." *Strahlentherapie*, **32**, 1–38.

Gray, L. H. 1936. "An Ionization Method for the Absolute Measurement of X-Ray Energy." *Proc. Roy. Soc. London*, **(A)**, **156**, 578–596.

Grebe, L. 1926. "Die energetische Bedeutung der R—Einheit." *Strahlentherapie*, **22**, 438–443.

Henshaw, P. S. 1944. "Roentgen Rays and Gamma Rays: Biological Effects." Glasser's *Handbook of Medical Physics*, 1352–1360, Chicago: Year Book Publishers.

Hill, C. G. A. 1946. "Uniform Luminescent Materials." *Science*, **103**, 155–158.

Holthusen, H. 1920. Über die biologische Wirksamkeit von Röntgenstrahlen verschiedener Wellenlänge." *Fortschr, d. Röntgenstr.* **27**, 183–244.

Holthusen, H. 1921. "Beiträge zur Biologie der Strahlenwirkung. Untersuchungen an Askarideiern." *Pflüger's Arch. f. Physiol.*, **187**, 1–24.

Jordan, P. 1941. "Über die Spezifität von Antikörpern, Fermenten, Viren, Genen." *Naturwissenschaften*, **29**, 89–100.

Kirchner, F. 1930. "Allgemeine Physik der Röntgenstrahlen." *Handbuch d. Experimentalphysik*, **24**, I.

Koyenuma, N. 1942. "Trefferwahrscheinlichkeit und Variabilität." *Naturwissenschaften*, **30**, 732–733.

Koyenuma, N. 1943. "Beiträge zur Theorie der biologischen Strahlenwirkung." *Zeit. f. Physik*, **120**, 185–211.

Lauritsen, C. C. 1933a. "Energy Considerations in High Voltage Therapy." *Amer. Jour. Radiology and Radium Therapy*, **30**, 380–387.

Lauritsen, C. C. 1933b. "Energy Considerations in Medium and High Voltage Therapy." *Amer. Jour. Radiology and Radium Therapy*, **30**, 529–532.

Liechti, A. 1929. "Über den Zeitfaktor der biologischen Strahlenwirkung." *Strahlentherapie*, **33**, 1–54.

Mayneord, W. V. 1938. "The Use of X-Rays and γ Rays in Medicine." *Reports on Progress in Physics*, **V**, 284–301.

Mayneord, W. V. 1940. "Energy Absorption." *Brit. Jour. Radiology*, **13**, 235–247.

Möglich, F., R. Rompe, and N. W. Timoféeff–Ressovsky. 1942. "Bemerkungen zu physikalischen Modellvorstellungen über Energieausbreitungsmechanismen im Treffbereich bei strahlenbiologischen Vorgängen." *Naturwissenschaften*, **30**, 409–419.

Mottram, J. C. 1913. "On the Action of Beta and Gamma Rays of Radium on the Cell in Different States of Nuclear Division." *"Archives of Middlesex Hosp."* **30**, 98–119

Noddack, W. 1926. "Photochemie." *Handbuch d. Physik*, **23** (1). Berlin: J. Springer.

Opatowski, I. 1942. "An Inverse Problem Concerning a Chain Process." *Proc. Nat. Acad. Sci., U. S. A.*, **28**, 83–88.

Opatowski, I. 1945a. "Markoff Chains with Reverse Transitions." *Proc. Nat. Acad. Sci., U. S. A.* **32**, 411–414.

Opatowski, I. 1945b. "Chain Processes and Their Biophysical Applications. Part I: General Theory." *Bull. Math. Biophysics*, **7**, 161–180.

Opatowski, I. 1946. "Chain Processes and Their Biophysical Applications. Part II. The Effect of Recovery." *Bull. Math. Biophysics*, **8**, 7–15.

Pearson, K. 1934. *Tables of the Incomplete Γ-Function.* Cambridge: University Press.

Perthes, G. 1904. "Versuche über den Einfluss der Röntgenstrahlen und Radiumstrahlen auf die Zellteilunge." *Deutsche Med. Wochenschrift*, 632–634, 668–670.

Richtmyer, I. K., and E. H. Kennard. 1942. *Introduction to Modern Physics.* New York: McGraw-Hill.

Rump, W. 1927. "Energiemessungen an Röntgenstrahlen." *Zeit. f. Physik*, **43**, 254–298.

Ruppert, W. 1924. "Empfindlichkeitsänderungen des Ascariseies auf verschiedenen Stadien der Entwicklung gegenüber der Einwirkung ultravioletter Strahlen." *Zeit. f. wiss. Zool.* **123**, 103–155.

Schelling, v. H. 1942. "Trefferwahrscheinlichkeit und Variabilität. Ein Versuch zur Deutung der Wirksamkeit von Antigenen." *Naturwissenschaften.* **30**, 306–312.

Schleip, W. 1923. "Die Wirkung des ultravioletten Lichtes auf die morphologischen Bestandteile des Ascaris-Eies." *Arch. f. Zellforschung*, 17, 289–367.
Scott, C. M. 1937. "Some Quantitative Aspects of the Biological Actions of X and γ Rays." *Medical Research Council*, Special Report No. 223.
Stevens, N. M. 1909. "The Effect of Ultraviolet Light upon the Developing Eggs of Ascaris Megalocephala." *Arch. f. Entw.-Mech. d. Organ.*, 27, 622–639.
Victoreen, J. A. 1944. "Roentgen Rays: Absorption and Scattering." Glasser's *Handbook of Medical Physics*, 1330–1335. Chicago: Year Book Publishers.
Webster, D. L. 1933. "Roentgen-Ray Physics." Glasser's *Science of Radiology*, Springfield, Ill.: Ch. C. Thomas.
Zuppinger, A. 1928. "Radiobiologische Undersuchungen an Ascariseiern." *Strahlentherapie*, 28, 639–758.

BULLETIN OF
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ON THE RELATIONSHIP BETWEEN RESPONSE TIME AND DOSAGE OF A DRUG AS A FUNCTION OF ITS MODE OF ENTRY[1]

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Theoretical studies have been carried out to determine the effect of the route of entry and the temporal sequence of dosage on the response. On the basis of continuity equations applied to a schematized system, equations relating the dosage and response time have been derived for some special cases, and the form of this relationship is discussed.

The effect of any material taken into the system of an organism is in general very complex and some of the effects produced mutually interact. We shall consider the relatively simple case where the response is not appreciably influenced by the other effects produced.

We shall use the following abstraction. The material, whose effect is to be observed, enters some part of the organism, is transported to the blood and subsequently is enabled to pass into a particular region where the response is produced. We shall assume that the function of one such region dominates the outcome.

Let the amount of the chemical in the organ of entry at time t be $M(t)$, in the blood—$m(t)$, and in the sensitive organ—$x(t)$. Let the rate of entry into the blood, regardless of the path of entry be $R(t)$. If γm is the rate of transfer of the substance into the sensitive region, and bm is the rate of transfer of m into any other region plus any inactivation in the blood, then the value of $m(t)$ is determined from the continuity equation

$$\frac{dm}{dt} = R(t) - bm - \gamma m. \tag{1}$$

We shall assume, as a first approximation, that b and γ are constants thereby neglecting the possibility for a threshold of elimination as well as the reverse flow from the various organs.

[1] This paper is based in part on work done for the Office of Scientific Research and Development under Contract NDCrc-132 with the University of Chicago.

Similarly, if βx is the inactivation rate in the sensitive organ, we have for the determination of x, the expression

$$\frac{dx}{dt} = \gamma m - \beta x. \tag{2}$$

If the return flow from the various regions is not neglected, the above equations are replaced by a set of equations involving all the regions. Let the subscript i refer to the ith region, exclusive of the sensitive region, in which there is a concentration c_i of the substance administered. Let α_i be the partition coefficient for cellular fluid of a region with respect to blood multiplied by the blood volume. If β_i is an inactivation rate per unit concentration and b_i is the product of the equivalent permeability and the effective area multiplied by the ratio of the volume of the region to that of the blood, then we have the equations

$$\frac{dm}{dt} = R(t) - \sum_i b_i (m - \alpha_i c_i), \tag{3}$$

$$\frac{dc_i}{dt} = b_i (m - \alpha_i c_i) - \beta_i c_i, \tag{4}$$

together with an equation in x similar to equation (4).

If the response to be studied is graded then we may suppose that the degree of response is some simple function of the quantity x. A more complex relationship will be considered subsequently. We shall consider an all or none type of response on the assumption that the quantity of the material in the sensitive region determines the response. Let $\bar{x}_j$ be the threshold value of x for the response to be produced in the jth individual of a population, and let $\bar{x}$ be the median value of the $\bar{x}_j$'s. Let t_0 be the time required for the response to be observed after the time T, for which $x(T) = \bar{x}$, together with any other constant time delays. It will be understood that t_0 is properly accounted for, so that it need no longer be written explicitly.

The individual thresholds, $\bar{x}_j$, are distributed in some manner over the population. Empirically it is found that for many responses the distribution is made very nearly a normal error function if the logarithm of the variable is used. Let $p(z)$ be the normal error function and define $P(y)$ by

$$P(y) = \int_{-\infty}^{y} p(z)\, dz. \tag{5}$$

Then, if λ is the standard deviation, we have assumed that

$$y = \frac{1}{\lambda} \log x/\bar{x}, \tag{6}$$

as $\bar{x}$ was defined as the median value of the $\bar{x}_j$'s. Since x is a function of t, P is also a function of t as well as of some measure of the dosage.

We shall now consider the effect of several modes of entry.

(a) If the rate of entry into the organ of entry is constant (e.g., constant injection, constant breathing of material coming in through the lungs), then the rate will be roughly proportional to the external concentration C. Thus $R = H(C - m) = HC$ if $C >> m$. If C is a known function of time $C(t)$, it is still possible to solve equations (1) and (2), with the initial conditions $m = x = 0$ for $t = 0$.

For this case the response is observed at a time $T + t_0$, where T is determined from $x(T) = \bar{x}$, $x(t)$ being determined from equations (1) and (2) with $R = HC$. This would imply an exposure to C for a time T, that is, t_0 units of time less than that necessary to produce the response. But according to the above assumptions, the response has already been set in motion; thus, continuation of the exposure can, at most, increase the per cent which responds. In case the exposure is stopped at T, or t_0 seconds before the response is observed, then if HC is constant, the relationship between T and C is determined from

$$\begin{aligned}(b + \gamma)\beta(\beta - b - \gamma)\,\bar{x} = {} & (\beta - b - \gamma)\gamma HC(1 - e^{-\beta T}) \\ & - \gamma\beta HC(e^{-(b+\gamma)T} - e^{-\beta T}).\end{aligned} \tag{7}$$

For small T and large C, $CT^2 = 2\bar{x}/\gamma H$, and thus the quantity CT for median response becomes large for small T or large C. If the exposure continues to $T + t_0$, this effect is only accentuated. If, however, exposure is only for a time τ, chosen so that after a total time $T + t_0$ a median response is obtained, then $C\tau$ is a constant for small τ. The quantity $C\tau$ may remain approximately constant over a considerable range of values of τ. Similarly for not too small or too large T, CT is approximately constant.

For long times or small C, $CT \approx C\tau$ becomes large. If $C \leqq \beta(b + \gamma)/\gamma H$, then the response never occurs in more than half the population, and generally will not occur in any individual for small enough C.

(b) If a dose D is impulsively given into some region and if δM is the rate of entry into the blood stream, and εM is the inactivation rate in the organ of entry, then

$$\frac{dM}{dt} = -(\delta + \varepsilon)M, \tag{8}$$

where $M = D$ for $t = 0$. From equation (8), we have

$$M = De^{-(\delta+\varepsilon)t}, \tag{9}$$

and thus

$$R(t) = \delta M = \delta De^{-(\delta+\varepsilon)t}. \tag{10}$$

In this case equations (1) and (2) are solved with $m = x = 0$ for $t = 0$. Solving these equations and setting $x = \bar{x}$ for $t = T$, then T is determined from

$$(b + \gamma - \delta - \varepsilon)\,\bar{x} = \delta D\gamma \left(\frac{e^{-(\delta+\varepsilon)T} - e^{-\beta T}}{\beta - \delta - \varepsilon} - \frac{e^{-(b+\gamma)T} - e^{-\beta T}}{\beta - b - \gamma} \right) : \tag{11}$$

If D is too small, evidently no T satisfies equation (11), thus no response will be obtained for small enough D.

If D is very large, T very small, then $T = \sqrt{2\bar{x}/\delta\gamma D}$ and thus T increases very slowly as D decreases. The above result cannot be readily verified because of the variability of t_0.

(c) If the material is injected directly into the blood stream at a rate R which may be a function $R(t)$, then equations (1) and (2) can be solved directly with $m = x = 0$, for $t = 0$.

The results, for constant R, are the same as for case (a), if HC is replaced by R. In this case again the result depends upon whether the injection is continued until the response occurs or continued until some time τ, such that some time later, $T + t_0 - \tau$, a median response is observed. In the first instance the total dose $D = RT$ becomes infinite for large R. In the later case the dose $D = R\tau$ remains finite. For small R, D becomes infinite and if $R < \beta(b + \gamma)/\gamma$ no median response occurs. To determine $D(\tau)$, first solve for $x(\tau)$ as in equation (7), and for $m(\tau)$ from equation (1), and determine $x(t)$ for $t > \tau$ from equations (1) and (2) with $R = 0$ and $m = m(\tau)$ and $x = x(\tau)$ for $t = 0$ as initial conditions. Differentiating $x(t)$ with respect to t and setting the result equal to zero, the time $T(\tau, R)$ can be obtained. For this value of the time the quantity x has reached its median threshold so that $x[T(\tau, R)] = \bar{x}$. This is an implicit relationship between R and τ, or since $D = R\tau$, we have the relationship $D(\tau)$. Moreover since T is already determined, D determines τ and T.

(d) If the total amount D of material is injected very rapidly into the blood stream, then equations (1) and (2) are solved with $R = 0$ but with $m = D$, $x = 0$ for $t = 0$. This leads to the equation

$$(\beta - b - \gamma)\,\bar{x} = \gamma D(e^{-(b+\gamma)T} - e^{-\beta T}), \tag{12}$$

for determining the relationship between T and D. If D is too small there will be no response. If D is sufficiently large then $T = \bar{x}/\gamma D$. For both cases (b) and (c) the threshold dose D_m can be obtained by

setting the quantity in parentheses on the right-hand side equal to its maximum value and solving this equation for $D = D_m$.

Case (d) can be considered a special case of (c) for which R is large and τ small, but such that $R\tau = D$, the total dose.

(e) If the critical organ is directly perfused with the chemical at a concentration C or if the organism under observation is unicellular, then $x(t)$ is determined from equation (2) with γm replaced by γC where γ is the permeability times the effective area divided by the volume. In this case, if C is constant, $C(T)$ can be solved for T and written as

$$T = T' - t_0 = -\frac{1}{\beta}\log\left(1 - \frac{\beta\bar{x}}{\gamma C}\right). \tag{13}$$

In each of the above cases if x is identified with the response measured, then $x(t)$ is determined for the various cases by replacing T by t and $\bar{x}$ by x.

Cases (c), (d), and (e) are determined by the three parameters β, $(b + \gamma)$ and $\bar{x}/\gamma$. With the additional parameter H, case (a) is also specified, whereas ε and δ given in addition to the first three parameters, case (b) is also determined.

For each of the above cases, we can determine, by equations (5) and (6), the relationship $P[y(D, t)]$. This determines the per cent response within the time t if the dose is D.

If t is fixed, then y of equation (6) is linear in the logarithm of D, the slope being λ^{-1}, and the intercept depending upon the value of t. If D is fixed, then y can be considered to be a function of t with D as a parameter. In the cases which can be approximated by equation (14) then, for not too large t, y is approximately linear in the logarithm of t, the slope being again λ^{-1}, and the intercept increasing with D. For larger t, the curves become concave downwards, approaching a limit. On the other hand, if equation (14) cannot be used, then the slopes of y of log t for not too large t, may no longer be λ^{-1}. But in either case the results are complicated by the variability of t_0.

In equation (12) if β and $(b + \gamma)$ are far from equal and if a is a number equal to the larger, then to a fair degree of approximation the time T is given by equation (13) with β replaced by a and C replaced by D. From this, T approaches infinity as D approaches $D_m = a\bar{x}/\gamma$. Experimentally equation (13) is almost indistinguishable from

$$(T' - t_0)\,(D - D_m)^n = \kappa, \tag{14}$$

if $\kappa = \bar{x}/\gamma$ and $n = 1$, especially if t_0 is slightly changed (cf. J. Ipsen, 1941). Furthermore, even if β and $(b + \gamma)$ are comparable, equa-

tions (12) and (14) are experimentally almost equivalent, the principle difference being that in equation (12), T cannot exceed some large value T_m for $D = D_m$ whereas in equations (13) and (14) $T_m = \infty$. This, however, is experimentally difficult to determine.

Equation (7) is similarly almost equivalent to (14) whereas equation (11) may not be. If any one of the quantities β, $(b + \gamma)$, and $(\delta + \varepsilon)$ is considerably larger than the others, then equation (11) may be approximated by equation (14) for $n = 1$, with a new value of t_0 which depends slightly upon D and which reduces very slowly to t_0 for very large D. For practical purposes, this means that the observed t_0 may include a time delay which is only roughly constant. If, for example, all three quantities are equal to a, then instead of expression (11), we have

$$2\bar{x} = \delta\gamma DT^2 e^{-aT}. \tag{15}$$

In this case, with an adjustment on D_m, a fairly satisfactory approximation is given by equation (14) with $n = 1/2$ and $\kappa = \sqrt{2\bar{x}/\gamma\delta}$ except for D very near D_m.

From the above results it would be expected that the relationship between dose and response time could be represented in many instances by equation (14) in which $n = 1$ and in most instances if n is some fraction. However, this would be based on the assumption that the instantaneous value of x determines the response. We shall now consider a more realistic picture.

Let the critical organ normally produce the total amount F of some substance which is the quantity to be measured or which is adequate to produce the response to be observed. The quantity F will, in general, be determined from a continuity equation which has the form

$$\frac{dF}{dt} = G - gF, \tag{16}$$

where G and g are, in general, functions of F, as well as the concentrations of many other substances. Even if G and g are assumed to be constant as a first approximation, any impressed change in F from its equilibrium value $F_0 = G/g$ results in a spontaneous return to that equilibrium. Equation (16) is the simplest equation representing the property of homeostasis. In particular G or g must depend upon x. If F is produced outside the critical organ, then G is the rate of entry extrapolated to $F = 0$ while gF is the return flow due to $F \neq 0$ plus any inactivation. In this case it would be expected that G may be fairly independent of x whereas g in a first approximation would be given by $g = g_0 + rx$, that is, the removal of F due to x would take

place at a rate proportional to x and to F.

If F is produced in the critical organ, then either G or g may depend upon x. If the effect of x is to reduce F then $g(x)$ may in a first approximation be of the form $g = g_0 + rx$ over a wide range of x, whereas $G(x)$ in the form $G_0 - k'x$ would be expected to hold only for a limited range of values of x. If x acts to increase F then to a first approximation g would probably be independent of x, whereas in this case G could be represented by $G = G_0 + kx$ as a first approximation.

If g is a constant and $G(x) = G_0 + kx$ then for case (d) we have an equation similar to equation (11). The equation for $D(T)$ in this case is obtained from (11) if β is replaced by $(b + \gamma)$ and $\bar{x}$ is replaced by $(\bar{F} - F_0)/k$, $\bar{F}$ being the threshold for the response to be observed.

If, on the other hand, we consider that x acts to decrease F, the result would be the same if $\bar{F} < F_0$ and $F_0 - \bar{F} << F_0$. This latter inequality is rather unlikely. It is more likely that the function of the critical organ must be reduced to at least one-half or even to a much smaller function, so that the approximation $G = G_0 - k'x$ would be of little value. Even if for each physiological unit G could be represented by $y = G_0 - k'x$ for $x < G_0/k'$, $y = 0$ for $x > G_0/k'$, the fact that not all would have exactly the same parameters results in F gradually approaching zero. In writing equation (2) for x we have assumed essentially an infinite internal diffusion coefficient. To a first approximation, removal of this restriction simply subtracts a constant from x. Thus $F(x)$ for $t \to \infty$ could be represented by a curve horizontal at $x = 0$, having an inflection point, and which then gradually approaches zero, though being zero for some very large x. But if the interest is only in the response produced when $F = \bar{F}$, with F_0 several times $\bar{F}$, then the shape of $F(x)$ for near F_0 may be of no interest. Furthermore in a quantized response only the time at which $F = \bar{F}$ is of interest. This tends to reduce the effect of changes in the form of $F(x)$ on the $D(T)$ relationship. Nevertheless, it may be that the final relationship between D and T is no longer approximately given by equation (14) for $n \leqq 1$.

LITERATURE

Ipsen, I. 1941. *Contribution to the Theory of Biological Standardization.* Copenhagen: Nyt Nordisk Forlag, Arnold Busck.

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